



The relationship between subjective well-being and dopamine D₂ receptors in patients treated with a dopamine partial agonist and full antagonist antipsychotics

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Abstract

Antipsychotic drugs produce unpleasant subjective experiences, which have been associated with high levels of dopamine D₂ receptor occupancy. Aripiprazole is a partial agonist antipsychotic, which is hypothesized to produce a different subjective experience profile compared to standard D₂ antagonist antipsychotics. The aim of this study was to compare the effect of D₂ occupancy produced by a partial agonist antipsychotic (aripiprazole) to that of antagonist antipsychotics (risperidone or olanzapine) on the subjective well-being of patients. Subjective well-being was measured using the Subjective Well-being under Neuroleptics Scale (SWN) and was related to dopamine D₂ receptor occupancy using [¹¹C]raclopride PET. Patients that were switched to aripiprazole showed improvement in their subjective well-being from 79.80 (s.d. = 16.08) to 89.90 (s.d. = 15.33), an effect that was sustained for 6 months. This sustained improvement was observed despite very high levels of DA D₂ occupancy (82–99%), in contrast to the effects of antagonist antipsychotics on subjective well-being.

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Introduction

Antipsychotic medications have been the first-line treatment for psychosis in schizophrenia and other psychotic disorders for nearly half a century; and the most important predictor of clinical outcome is adherence with antipsychotic medication (Karow *et al.* 2007). However, patients dislike taking the medications and usually stop them (Marder, 2005). In recent years, the blockade of the dopamine (DA) system has been associated with these adverse subjective experiences (see Voruganti & Awad, 2004 for review). In addition, α -methyl paratyrosine (AMPT) – an agent

which blocks tyrosine hydroxylase and decreases DA levels temporarily – has been shown to produce reversible dysphoria, and decreases in happiness and tiredness in healthy volunteers (Verhoeff *et al.* 2001, 2003) and patients with schizophrenia (Voruganti *et al.* 2001). Further, it has been demonstrated that high levels of dopamine D₂ (DA D₂) blockade are associated with dysphoric experiences (de Haan *et al.* 2003, 2004) or depression (Bressan *et al.* 2002) in patients with psychosis treated with antipsychotic medications. Consistent with these observations, we recently replicated these original findings and furthermore implicated extrastriatal brain regions (temporal and insular cortex) in subjective dysphoria produced by risperidone or olanzapine (Mizrahi *et al.* 2007). Taken together these data suggest that a disruption of the DA system through antagonism of striatal and/or extrastriatal DA D₂ receptors may play an important role in adverse subjective experiences attributed to antagonist antipsychotics.

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Aripiprazole, a D_2 partial agonist, differs from previous typical and atypical antipsychotics in its molecular actions at the DA D_2 receptors. Clinically effective antipsychotic doses of 10–30 mg/d aripiprazole in patients with schizophrenia show a low propensity for extrapyramidal side-effects or prolactin elevation (Burris *et al.* 2002; Kane *et al.* 2002) despite very high D_2 receptor occupancy (Mamo *et al.* 2007; Yokoi *et al.* 2002). The effect of aripiprazole on subjective well-being has not been previously investigated, and given the impact of subjective well-being on adherence to antipsychotic medication, we decided to investigate the neurobiological underpinning of aripiprazole on subjective well-being. While the high D_2 occupancy of aripiprazole might be expected to predict worse subjective experience, the partial agonist profile at D_2 receptors might be expected to mitigate this effect.

Methods

The data collection was undertaken at the Centre for Addiction and Mental Health (CAMH), Toronto and was approved by the CAMH Review Ethics Board, all subjects provided written informed consent. This study included a group of patients willing to switch to aripiprazole – a partial agonist antipsychotic ($n=11$), and a comparison group of patients that had been on stable doses of antagonist antipsychotics (olanzapine or risperidone, $n=11$) for >4 months. Subjects participating in the aripiprazole arm of the study participated in a PET study designed to study the occupancy profile of aripiprazole on DA and serotonin receptors; details including antipsychotic switching procedures have been previously reported (Mamo *et al.* 2007). Briefly, they were randomized to 10, 15, 20 or 30 mg aripiprazole and then followed for 6 months. Clinical evaluations as well as imaging analysis procedures were comparable for both groups. However, a longitudinal arm is only available for the partial agonist group.

Diagnosis was confirmed using the Mini International Neuropsychiatric Interview. Given that the aripiprazole group included a longitudinal arm, the following clinical assessments were completed at baseline and then weekly for the first 4 wk, with a final visit at 6 months: Clinical Global Impression Scale (CGI), Simpson–Angus Scale (SAS), Barnes Akathisia Scale (BAS) and the Abnormal Involuntary Movement Scale (AIMS). Subjective well-being was measured with the Subjective Well-being under Neuroleptics Scale (SWN) – short version, which has five subscales: (a) mental functioning, (b) self-control, (c) emotional

regulation, (d) physical functioning, (e) social integration. Items are clearly formulated and easy to understand so that even the most cognitively disturbed patients are able to complete the questionnaire within 5–10 min (Naber *et al.* 2001). The SWN – short version has shown adequate psychometric properties (Cronbach's α -coefficient 0.92; Naber *et al.* 2001). The Positive and Negative Symptom Scale (PANSS; Kay *et al.* 1987), was administered at baseline and at the following 2 wk and 4 wk with a final visit at 6 months. For both groups the same psychopathological measures were obtained the day of the PET scan.

Statistical analysis of the clinical data was performed using repeated-measures analysis of variance with mixed models for the longitudinal portion of the study. Bonferroni-adjusted pair-wise comparisons were used as *post-hoc* tests. General linear models were used to relate the clinical variables with the PET data. All statistical analyses are two-tailed with $p < 0.05$.

All patients completed a [^{11}C]raclopride scan at expected peak plasma levels of aripiprazole olanzapine or risperidone (3–5, 6 and 2 h after the last pill respectively), using a CPS-HRRT high-resolution neuro-PET camera system (CPS Inc., USA) measuring radioactivity in 207 brain sections with a thickness of 1.2 mm each. Transmission scans using ^{137}Cs were used to correct for attenuation of the emission scans. A saline solution of 10.09 ± 0.7 mCi [^{11}C]raclopride with a specific activity at time of injection of 1598 ± 350 mCi/ μmol was injected as a bolus into an intravenous line placed in an antecubital vein. Emission data were acquired in list mode during 60 min. PET scans for the aripiprazole arm were carried out following at least 2 wk continuous aripiprazole treatment.

Subjects undertook a standard fast-spin echo with a proton density image acquired on a 1.5 T Signa-GE scanner. The regions of interest (ROI) were dorsal caudate (DCA), dorsal putamen (DPU), ventral striatum (VST) and cerebellum (Mawlawi *et al.* 2001), which was used as reference region. Time–activity curves (TACs) were obtained from the dynamic PET images in native space with reference to co-registered MRI image using the in-house software validated for obtaining semi-automated delineation of ROIs (Rusjan *et al.* 2006). In order to calculate receptor occupancy, data obtained from age- and sex-matched healthy controls (23 controls with [^{11}C]raclopride), using the same PET and MRI protocols, were used as an estimate of the subjects' unmedicated baseline. This approach is justifiable as previous studies have not shown a major effect of illness on [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) (Farde *et al.* 1987). BP_{ND} were obtained using the Simplified

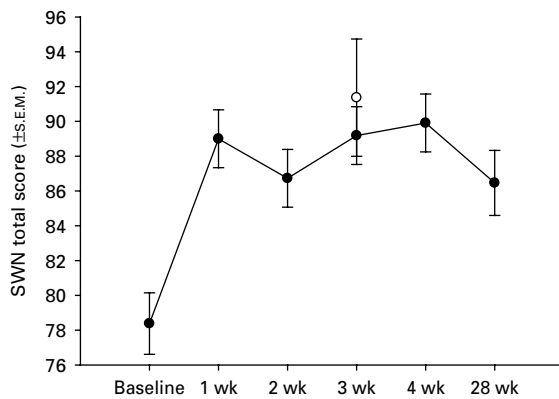


Fig. 1. Subjective Well-being under Neuroleptics Scale (SWN) score following the initiation of aripiprazole compared to SWN score in the full antagonist antipsychotic group. Subjective well-being change as indexed by the SWN total score following the initiation of partial agonist (aripiprazole; —●—), and full antagonist (—○—) antipsychotic groups.

Reference Tissue Model (SRTM; Lammertsma & Hume, 1996). Occupancy was calculated using the following formula:

$$(\text{BP}_{\text{ND, control}} - \text{BP}_{\text{ND, drug scan}}) / \text{BP}_{\text{ND, control}} \times 100.$$

Results

Twenty patients with a diagnosis of schizophrenia and two with schizoaffective disorder participated in the present study. Eleven patients were switched to aripiprazole and 11 patients had been taking either risperidone or olanzapine for >4 months at the time of the PET scan. The DA partial agonist antipsychotic (aripiprazole) group had a mean age of 31 yr (s.d. = 6.89 yr), and the antagonist antipsychotic group had a mean age of 36 yr (s.d. = 7.03 yr) ($t=1.8$, d.f. = 20, $p=0.08$). Before the switch to aripiprazole, patients were either off medication ($t=2$), on risperidone ($t=5$, 3–6 mg/d), olanzapine ($t=3$, 10–15 mg/d), or clozapine ($t=1$, 100 mg/d). At the time of the PET scan there was no difference between the groups for any of the psychopathological measures (PANSS positive: $t=0.14$, d.f. = 20, $p=0.88$; PANSS negative: $t=1.8$, d.f. = 20, $p=0.08$; PANSS general: $t=0.6$, d.f. = 20, $p=0.55$; PANSS total: $t=1.01$, d.f. = 20, $p=0.32$). However, the groups differed in their akathisia score ($t=-2.23$, d.f. = 20, $p=0.03$), with the aripiprazole group showing more akathisia than the antagonist antipsychotic group (side-effects discussed in detail in Mamo *et al.* 2007). Some patients in the antagonist antipsychotic group ($t=2$) were concomitantly taking benzodiazepines. The average dose of aripiprazole

was 18.75 mg (s.d. = 7.72), and the dosages for olanzapine and risperidone were 17.85 mg (s.d. = 7.83) and 1.87 mg (s.d. = 0.88), respectively.

Within the study period (6 months) SWN total score significantly improved ($F=6$, d.f. = 5, 47, $p=0.0002$), with the main effect observed during the first week ($t=44.37$, d.f. = 47, Bonferroni adjusted $p=0.001$) and remained unchanged at 6 months (Fig. 1). PANSS positive score did not change at any time during the study period ($F=2.04$, d.f. = 3, 29, $p=0.13$), and PANSS negative initial improvement was not sustained at 6 months ($F=1.75$, d.f. = 3, 29, $p=0.17$). However, PANSS general significantly improved initially and was maintained at 6 months ($F=5.38$, d.f. = 3, 29, $p=0.004$) (see Table 1).

The measured D₂ occupancies for the aripiprazole-treated patients ranged from 82% to 99%. However, the range of those treated with antagonist antipsychotics ranged from 57% to 89%. Aripiprazole showed higher occupancy in all regions of the striatum than antagonist antipsychotics (see Table 2).

SWN total score was not associated with striatal D₂ occupancy in those treated with aripiprazole in any subregion of the striatum ($r=-0.43$, $p=0.18$; $r=0.01$, $p=0.96$; $r=-0.52$, $p=0.09$ for the DCA, DPU, VST, respectively). As expected, striatal D₂ occupancy was significantly associated with those treated with antagonist antipsychotics in the VST ($r=-0.63$, $p=0.04$), but not associated in the DPU ($r=-0.55$, $p=0.07$) or DCA ($r=-0.50$, $p=0.11$) (Fig. 2).

Since occupancy is a derived measure, i.e. it is obtained after correcting individual measured BP_{ND} for estimated baseline levels, we wanted to examine if the BP_{ND} data from patients also correlated with SWN. The data showed that SWN total score was significantly associated with VST BP_{ND} ($r=0.63$, $p=0.04$), but not with the DCA ($r=0.50$, $p=0.11$) or DPU BP_{ND} ($r=0.55$, $p=0.07$) of those treated with antagonist antipsychotics. Similar to the occupancy data there was no significant association between SWN and BP_{ND} in those treated with aripiprazole in any region ($r=-0.41$, $p=0.20$; $r=-0.01$, $p=0.95$; $r=-0.47$, $p=0.14$ for the DCA, DPU, VST, respectively). These results are consistent with the occupancy data.

Discussion

To our knowledge this is the first study to investigate subjective well-being with aripiprazole (or any other partial agonist) and its association with D₂ receptor-binding potentials and occupancy. First, we report a putative early and sustained improvement in subjective well-being in patients switched to aripiprazole.

Table 1. Clinical measures following the switch to aripiprazole

Measures	Initial visit (s.d.)	4 wk aripiprazole (s.d.)	Statistical analysis (mixed models)
CGI	3.33 (0.94)	2.9 (0.79)	$F = 1.78$ d.f. = 22.3 $p = 0.17$
PANSS			
Total	51.4 (12.44)	42.75 (8.10)	$F = 10.58$ d.f. = 21.2 $p = 0.0007$
Positive	12.50 (5.28)	10.45 (10.23)	$F = 2.84$ d.f. = 21.2 $p = 0.08$
Negative	12.33 (3.72)	9.18 (2.89)	$F = 7.31$ d.f. = 21.2 $p = 0.003^a$
General	27.58 (7.31)	21.63 (4.00)	$F = 11.26$ d.f. = 21.2 $p = 0.0005$
SAS	0.25 (0.86)	0.41 (0.90)	$F = 1.59$ d.f. = 44.4 $p = 0.19$
BAS	0.41 (1.44)	1 (1.4)	$F = 2.51$ d.f. = 44.4 $p = 0.05$
SWN(T)	79.80 (16.08)	89.90 (15.33)	$F = 7.33$ d.f. = 39.4 $p = 0.0002$

CGI, Clinical Global Impression Scale; PANSS, Positive and Negative Symptom Scale; SAS, Simpson–Angus Scale; BAS, Barnes Akathisia Scale; SWN(T), Subjective Well-being under Neuroleptics Scale (Total score).

^a Improvement not maintained at 6 months.

Table 2. Occupancy values for the antagonist and partial agonist antipsychotic groups

Measures	Antagonist antipsychotic (s.d.)	Partial agonist antipsychotic (s.d.)	Statistic (t , p)
Occupancy DCA	76.54 (8.99)	93.53 (5.55)	-5.18 , <0.001
Occupancy DPU	74.82 (9.39)	87.11 (3.57)	-4.01 , 0.001
Occupancy VST	76.26 (9.34)	91.65 (3.59)	-5.05 , <0.001

DCA, Dorsal caudate; DPU, dorsal putamen; VST, ventral striatum.

Second, in contrast to antagonist antipsychotics (de Haan *et al.* 2000, 2003, 2004, 2005) aripiprazole did not induce dysphoric effects even at very high levels of D₂ occupancy. Third, while the antagonist antipsychotics showed an inverse relationship between occupancy and SWN, aripiprazole did not.

The discussion presented herein needs to be understood within the limitations imposed by the design of the present study. First, we do not have subjects' own baseline PET data which introduces some error in the estimated occupancy. However, we present concordant finding with the BP_{ND} estimates and sex- and age-corrected occupancy values, and hence this should not detract from the conclusions drawn in this study. Second, the sample size in each subgroup was small. However, previous data that investigated the correlations between either AMPT- or antipsychotic-induced dysphoria showed effects that ranged from $r = 0.53$ (de Haan *et al.* 2000) to $r = 0.82$ (Voruganti *et al.* 2001). Using the standard 80% power and the conventional reliability to reject the null hypothesis (i.e. $p < 0.05$), the present study's sample was

adequate to detect a significant correlation between those ranges. In fact, the significant association between D₂ BP_{ND} and occupancy data with SWN found in the antagonist antipsychotic group can be seen as replication from earlier SPECT and PET studies (de Haan *et al.* 2000, 2003, 2004; Mizrahi *et al.* 2007). Finally, the subjective well-being improvement presented herein could be viewed in light of a sample selection bias. Aripiprazole is not marketed in Canada, and the potential hope among patients receiving a 'special' drug not otherwise available, may have influenced our results. Importantly, subjects were not randomized to treatment groups, possibly biasing the clinical results of the present study. However, the SWN scores were still elevated and stable at 6 months, so that even if this was a placebo effect, the effect was certainly sustained. Future studies should use a blinded randomized design and careful monitoring of medication adherence (i.e. with serum aripiprazole concentrations (Gründer *et al.* 2008) to properly test the clinical findings of the present study. Finally, patients were blind to their occupancies and BP_{ND} and

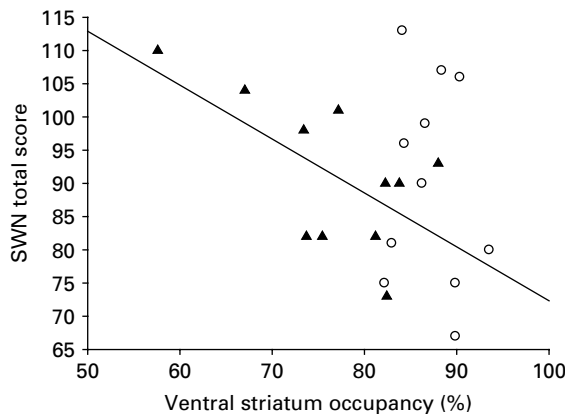


Fig. 2. Association between Subjective Well-being under Neuroleptics Scale (SWN) score and [¹¹C]raclopride DA D₂ occupancy in partial agonist-treated (aripiprazole; ○) vs. full antagonist antipsychotic-treated (risperidone or olanzapine; ▲) patients. No significant correlation between SWN score and D₂ occupancy value at the ventral striatum with partial agonist-treated patients; however, as expected, we found a negative association between DA D₂ occupancy in the ventral striatum and SWN in patients treated with antagonist antipsychotics.

thus could not have influenced the PET results presented.

The principal finding of this study is the observation of a significant improvement in subjective well-being, notwithstanding very high striatal DA D₂ occupancy. This contrasts with previous and present data on a series of antagonist antipsychotics: risperidone, olanzapine, and haloperidol (de Haan *et al.* 2000, 2003, 2004, 2005). The lack of relationship between DA D₂ occupancy and SWN may be related to the limited range of D₂ occupancy or may be due to the differential effects of partial vs. full antagonists on DA transmission. The more likely explanation is that in contrast to full antagonists (Bressan *et al.* 2002; de Haan *et al.* 2003, 2004; Mizrahi *et al.* 2007) a D₂ partial agonist antipsychotic would be expected to allow for physiological DA function and consequently may avoid adverse subjective experience and dysphoria and possibly even improve subjective experience, despite very high DA D₂ occupancy. Precisely how a partial agonist may decrease DA transmission to improve psychosis, and not impede transmission relevant for subject well-being is not clear. However, in animal studies it has been shown that a partial agonist like aripiprazole had a much higher ability to block amphetamine-induced locomotion (a measure of abnormal DA transmission) rather than spontaneous locomotion (a measure of endogenous and normal DA

transmission) (Natesan *et al.* 2006). Thus, DA partial agonist as well as the novel DA stabilizers may bring a distinctive (beneficial) effect on subjective well-being.

In the present study we also replicated earlier reports of the association between striatal D₂ occupancy and SWN using SPECT (de Haan *et al.* 2000, 2003, 2004) and PET (Mizrahi *et al.* 2007). The present results are also consistent with the studies that have shown that disruption of the DA function (temporarily, i.e. with AMPT) produce dysphoria, decrease happiness and provoke tiredness in healthy volunteers (Fujita *et al.* 2000; Verhoeff *et al.* 2003) and in drug-free schizophrenia patients (Voruganti *et al.* 2001). We extend those initial findings by confirming that the ventral portion of the striatum was shown to have a specific association with subjective well-being. The motor side-effects of antipsychotics are typically associated with the dorsal region of the striatum (Deutch *et al.* 1996). We find that the dysphoric effects correlate more specifically with the ventral portion of the striatum. This latter region is considered part of the 'limbic' circuitry and can be plausibly linked to a role in subjective well-being. The ventral portion of the striatum (which is thought to be the analogue of the nucleus accumbens in animals) is directly implicated in reward and motivation (Wise, 2002) and is key to many of the non-motor actions of antipsychotics in animals (i.e. conditioned avoidance response models) (Arnt *et al.* 1997). It is well documented that increased DA release in the nucleus accumbens is associated with the rewarding effects accompanying the acute administration of most drugs of abuse (Drevets *et al.* 2001). This putative dissociation between the association of the dorsal and ventral portion of the striatum BP_{ND} and occupancy data with subjective well-being may be related to the differential DA receptors distribution (i.e. D₂ predominates in the dorsal portion of the striatum, while D₃ in the most ventral portion), and may be key in the development of new antipsychotics (Sokoloff *et al.* 1990).

In conclusion, the present data suggests that aripiprazole may be associated with early and sustained improvement in subjective well-being, notwithstanding the very high D₂ occupancy. This may be related to its partial agonist profile at D₂ receptors. Given these findings, future controlled clinical studies, with aripiprazole and the other newly emerging partial agonists (e.g. bifeprunox), should make an effort to include subjective outcome as a variable of interest, particularly as it has recently been suggested that early improvement of subjective well-being is related to remission in first-episode schizophrenia (de Haan *et al.* 2008).

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Statement of Interest

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